

Sensations of skin infestation linked to abnormal frontolimbic brain reactivity and differences in self-representation

Article (Accepted Version)

Eccles, J A, Garfinkel, S N, Harrison, N A, Ward, J, Taylor, R E, Bewley, A P and Critchley, H D (2015) Sensations of skin infestation linked to abnormal frontolimbic brain reactivity and differences in self-representation. *Neuropsychologia*, 77. pp. 90-96. ISSN 0028-3932

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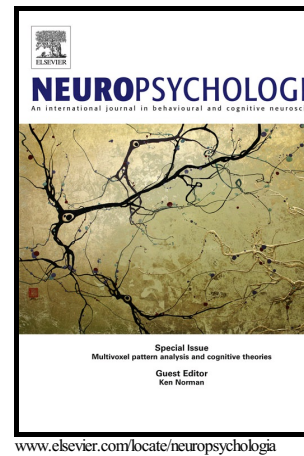
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Sensations Of Skin Infestation Linked To
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Differences In Self-Representation

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PII: S0028-3932(15)30122-6
DOI: <http://dx.doi.org/10.1016/j.neuropsychologia.2015.08.006>
Reference: NSY5690

To appear in: *Neuropsychologia*

Received date: 24 February 2015
Revised date: 31 July 2015
Accepted date: 6 August 2015

Cite this article as: J A Eccles, S N Garfinkel, N A Harrison, J Ward, R E Taylor, A P Bewley and H D Critchley, Sensations Of Skin Infestation Linked To Abnormal Frontolimbic Brain Reactivity And Differences In Self-Representation, *Neuropsychologia*, <http://dx.doi.org/10.1016/j.neuropsychologia.2015.08.006>

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1) TITLE: SENSATIONS OF SKIN INFESTATION LINKED TO ABNORMAL FRONTOLIMBIC BRAIN REACTIVITY AND DIFFERENCES IN SELF-REPRESENTATION

2) RUNNING TITLE: ABNORMAL SENSATIONS OF SKIN INFESTATION

3) Manuscript word count: 3,522

Number of tables: 2

Number of figures: 3

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7) This study was funded by the Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, UK and The Sackler Centre for Consciousness Science, University of Sussex, UK

8) No conflict of interest reported

9) Keywords: Psychodermatology, Delusional infestation, Neuroimaging, Rubber hand illusion, Interoception,

ABSTRACT

Some patients experience skin sensations of infestation and contamination that are elusive to proximate dermatological explanation. We undertook a functional magnetic resonance imaging study of the brain to demonstrate, for the first time, that central processing of infestation-relevant stimuli is altered in patients with such abnormal skin sensations. We show differences in neural activity within amygdala, insula, middle temporal lobe and frontal cortices. Patients also demonstrated altered measures of self-representation, with poorer sensitivity to internal bodily (interoceptive) signals and greater susceptibility to take on an illusion of body ownership: the rubber hand illusion. Together, these findings highlight a potential model for the maintenance of abnormal skin sensations, encompassing heightened threat processing within amygdala, increased salience of skin representations within insula and compromised prefrontal capacity for self-regulation and appraisal.

INTRODUCTION

A sub-group of patients presenting to dermatological services describe chronic abnormal skin sensations, characterised by a feeling of crawling or movement and sometimes stinging sensations on or under the skin in the absence of evidence for a local cause. These sensations can evoke the subjective experience and belief of infestation by animate organisms or infiltration by inanimate matter. If this belief is particularly strong, patients can be diagnosed as having Delusional Infestation (Bewley et al., 2010). Interestingly, although chronic abnormal skin sensations can occur in isolation, they are also observed secondary to other medical disorders, including stroke, dementia, intoxication or drug withdrawal states.

The impact of these experiences can be considerable, causing mood disorder, sleep disturbance and disruption of social or occupational functioning. Sometimes intense behaviours are pursued to target the putative infestation, including excessive bathing and cleaning of self and family (see (Freudenmann and Lepping, 2009) for examples). This constellation of symptoms and reactions are difficult to manage therapeutically although, for some, neuroleptic pharmacotherapy can be anecdotally useful (Huber et al., 2011, Bostwick, 2011, Ahmed and Bewley, 2013).

The central neurobiological mechanisms underlying the generation and maintenance of abnormal skin sensations of infestation remain unclear. There is a paucity of systematic neuroimaging work in this area. Heightened activation of bilateral somatosensory cortices is reported in one functional magnetic resonance imaging (fMRI) study of a single patient with firmly held beliefs regarding infestation (Geoffroy et al., 2013). Basal ganglia atrophy, chiefly localised to the putamen, is reported in an analysis of structural clinical MRI scans from nine patients with predominantly secondary abnormally skin sensations (Huber et al.,

2008). Further, the fronto-striato-thalamo-parietal network was implicated in two patients who underwent multimodal imaging (including FDG-PET and SPECT) (Freudenmann et al., 2010). Together, these neuroimaging studies suggest that abnormal skin sensations engage the same sensory regions as normal skin sensations yet are distinguished by abnormalities within executive and association cortices, and within dopamine-rich basal ganglia, regions supporting self-regulation and motivational drive.

The mismatch and misattribution of signals arising from the body is argued to be central to disorders of self-representation, and may be crucial to understanding symptom continuation in this group of patients. The *rubber hand illusion*, in which synchronous tactile and visual stimulation can evoke an individual to experience a false hand as his/her own (Tsakiris, 2010), is a useful experimental probe into mechanisms of self-representation and coherence. Individuals with conditions that impact on disordered self-representation (notably schizophrenia) are more susceptible to the illusion (Peled et al., 2000), as are healthy individuals scoring highly for psychosis proneness (Germine et al., 2012). The experience of illusory bodily ownership (engendered by ‘cross-modality binding’ between skin sensation and vision) is linked to *interoception*, i.e. the processing and interpretation of internal physiological signals (Tsakiris et al., 2011). Interestingly, on anatomical grounds, the sensation of itch is classified by some as interoceptive (Craig, 2003).

In order to gain insight into neural basis of infestation-like abnormal skin sensations, we undertook the first functional neuroimaging study to test the hypothesis that patients with these experiences will show dysfunctional central neural processing of affective and infestation-related stimuli. Viewing images of insects on skin is known to induce itchiness in a normative sample (Lloyd et al., 2013). We further tested the hypothesis that self-

representation is perturbed in these patients by characterising performance on two measures of self-representation: interoceptive accuracy and susceptibility to the rubber hand illusion.

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MATERIALS AND METHODS**Participants**

Six patients (mean age 51.8 years, 5 female) presenting with primary chronic abnormal skin sensations (of infestation or infiltration) were recruited from the specialist psychodermatology service at the Royal London Hospital (N=4) and from an outpatient clinic at Sussex Partnership NHS Trust (N=2). Patient demographics and phenomenology and illness characteristics are described in Table 1. Illness severity was established using a Visual Analogue Scale. Fifteen healthy controls matched for age and gender (mean age 43.0 years, 12 females) were also recruited. Three gender and approximate age matched controls were selected per participant (save one patient (F) who was a similar age and same gender to other patient and thus shared the matched controls of that patient). Age was not statistically significantly between the two groups ($t(19)=1.67$, $p = 0.11$). All participants provided written informed consent. The study was approved by the Brighton and Sussex Regional Ethics Committee.

Table 1 here

Neuroimaging**Neuroimaging experimental task**

Participants were placed on the scanner bed in a supine position. Visual stimuli were projected on a screen behind the scanner, which the participant could view through a mirror mounted in the head coil. A set of novel visual stimuli was produced, each consisting of an

object (insect, non-insect) overlaid on a background (skin, leaf) (Figure 1A-D). Neutral and disgust/fear images (from IAPS; International Affective Picture System) were additionally used as general control probes for affective processing. All images were presented in a randomized event-related experimental design as a single task. This strategy ensured the novelty of infestation-related images was retained, reducing effects of habituation. Second, IAPS images were chosen to inter-mix with our novel stimuli (which did not contain any images of skin) in order to characterise the patients in terms of non-specific (i.e. general non infestation-related) affective reactivity.

Each image was shown for 4000ms with an inter-trial interval of 1500ms, interspersed with randomly presented null events (central cross hair) totalling 24 % of all trials. There were 190 trials in total including null events, of which 60% comprised novel stimuli and 16% IAPS images. These trials were split into two equal runs to minimise scanner drift.

Imaging data acquisition

Whole-brain fMRI data were acquired on a 1.5 Tesla Siemens Avanto scanner. To minimise signal artefacts originating from the sinuses, particularly within ventromedial prefrontal / orbitofrontal regions, axial slices were tilted 30° from the inter-commissural plane. Thirty-six slices (3mm thick, 0.75 mm inter-slice gap) were acquired with an in-plane resolution of 3 x 3 mm (repetition time = 3300ms per volume, echo time = 50ms). Field maps were also acquired to enable subsequent unwarping of functional data with regard to the B0 field.

Imaging data analysis

fMRI data were analysed using statistical parametric mapping software (SPM8, www.fil.ion.ucl.ac.uk/spm) in MatLab R2012a (Mathworks). Spatial pre-processing was performed with realignment to the first volume, co-registration to the participant's high-resolution T1-weighted structural image, grey matter segmentation then normalisation to Montreal Neurological Institute (MNI) space. Resulting images were spatially smoothed with an 8-mm FWHM Gaussian Kernel. Voxel size was interpolated during pre-processing to isotropic 2 x 2 x 2 mm.

Individual participant (first level) analyses were performed using SPM8, modelling presentation of each stimulus type (both novel stimuli and IAPS images) as experimental effects of interest, while controlling for volume-by-volume movement (six regressors). Statistical maps of contrast estimates were entered into second-level group analyses. For the novel stimuli an individual 2x2x2 full-factorial model was used to analyse the results with the three factors: participant group (patient, control), object (insect, non-insect) and background type (skin, leaf). A further individual 2x2 factorial model was used to compare these earlier findings to responses evoked by IAPS stimuli: factors participant group (patient, control) and emotion (fear/disgust, neutral). Threshold significance was set using the cluster extent to manage multiple comparisons across the whole brain (Slotnick, 2008). 10,000 Monte Carlo simulations determined that clusters of 64 or more contiguous voxels activated at an uncorrected voxel-wise threshold of $p < 0.01$ ensured the probability of Type-1 statistical errors was below 0.05. Additionally functional activity in significant clusters was acquired for each subject; non parametric tests at a significance threshold of $p < 0.05$ were performed to look for significant differences in activity for each stimulus type (Mann Whitney); and correlation co-efficients (Pearson) used to determine significant correlations between functional activity in one area compared to another.

Behavioural tasks

Interoception

All measures of interoception were calculated in line with current literature (Garfinkel and Critchley, 2013, Garfinkel et al., 2015, Hart et al., 2013).

Interoceptive accuracy.

We used the mental tracking task (Schandry, 1981) to measure objective interoceptive accuracy, (Figure 1F). Each participant was connected to a NONIN8600 pulse oximeter (NONIN, Nonin Medical, Minnesota, USA) and judged, at rest, the number of heartbeats perceived over a set of time intervals, following instructions: ‘Without manually checking, can you silently count each heartbeat you feel in your body from the time you hear “start” to when you hear “stop”.’ The task was repeated 6 times, using time-windows of 25, 30, 35, 40, 45 and 50 s, presented in a randomised order. Interoceptive accuracy score for mental

tracking was calculated as $1 - \frac{|nbeats_{real} - nbeats_{reported}|}{(nbeats_{real} + nbeats_{reported}) / 2}$ (Hart et al., 2013, Garfinkel et al., 2015). Here, inclusion of $nbeats_{reported}$ in the denominator mitigated against overestimation of accuracy.

Interoceptive sensibility and interoceptive trait prediction error.

We also measured self-reported experience of interoceptive sensations and focus (interoceptive sensibility; Porges Body Perception Questionnaire (Porges, 1993). It tasks an individual to rate their personal experience of internal bodily sensations, and is has been used as a subjective measure of interoceptive sensibility (Garfinkel and Critchley, 2013, Garfinkel et al., 2015). The scale incorporates 45 bodily sensations (e.g. stomach and gut pains). Our

participants indicated their day-to-day experience of each sensation using a Likert scale ranging from ‘never’ to ‘always’. Each response was scored up to a maximum of five points (an answer of always gives a score of 5 points). We used the measure of interoceptive sensibility to test interoceptive trait prediction error (Garfinkel et al., 2015) This is the discrepancy between objective interoceptive accuracy (as determined by task performance) and subjective interoceptive sensibility (as determined by self-report). To determine this all scores were z transformed and the differences between z of interoceptive accuracy and z of sensibility were computed to quantify degree of error for group comparison.

Rubber hand illusion (RHI)

A modified version of standard protocols (Holle et al., 2011, Lloyd, 2007) was used to examine the *Rubber hand illusion*— using synchronous stroking only and non-rotated hands (due to time constraints). In this version the participant was seated at a table, facing the experimenter. On the table was a box, which was open to the sides, see Figure 1E. The participant was instructed to place his/her right hand at a marked position inside the box where it was concealed from their view. A rubber hand was also placed at a marked position inside the box, at a position approximately 20 cm to the right of the midline of the participant. The location of the participant’s real hand was at an additional 20 cm further to the right. This spatial arrangement of rubber hand and real hand is known to elicit a reliable illusion (Lloyd, 2007). The top cover of the box contained a hole, through which the participant could see the rubber hand but not her/his real hand. Before each trial, the rubber hand was concealed by placing an additional cover on top of the box. A ruler was placed on top of the box, and the participant was asked to indicate where he/she thought that his/her right index finger was located, by saying the corresponding number on the ruler (the prestimulus position). A different offset was used for the ruler in each trial to reduce memory effects. Next, the ruler

and the top cover were removed, and the rubber hand and the real hand were stroked by the experimenter with two identical paintbrushes. Stroking occurred horizontally on the index finger, from knuckle to finger tip and lasted for 1 min. Each stroke lasted approximately 500–1000 ms. The experimenter immediately repositioned the paintbrushes at the knuckle and began the next stroke some 500–1000 ms after the end of the previous stroke. Stroking was synchronous. Participants were asked to look at the rubber hand throughout the stroking period, which lasted for 60 s. After the stroking had finished, the top cover and ruler were again placed onto the box, and the participant was again asked to indicate the position of own right index finger (the poststimulus position).

Proprioceptive drift, an index of the illusion strength, was calculated by subtracting the pre-stimulus position from the post-stimulus position in cm. Participants also completed the short version of the rubber hand questionnaire (Longo et al., 2008), quantifying three different components of the experience of embodiment: ownership (five items), location (three items), and agency (two items) on a 7-point Likert scale ranging from -3 (“strongly disagree”) to +3 (“strongly agree”), with 0 being “neither agree nor disagree.”

Figure 1 here

RESULTS

Neuroimaging results: insect and skin images

A discrete set of regions was activated during the neuroimaging task (Table 2). Across groups, viewing insects compared to non-insects activated a region of fusiform cortex extending into middle temporal lobe.

Table 2 here

Figure 2 here

Across groups, the main effect of the background (skin v. leaf) enhanced activity within right posterior insular/S2 cortex. Within this region, patients showed strong activation to all stimuli depicted upon skin, ($U(21)=18$, $p=0.018$). Controls deactivated this region to non-insects on skin ($U(21)=21$, $p=0.033$)(Fig 2B).

Across all stimulus types, patients showed significantly greater responses within amygdala and parahippocampus compared to controls (main effect of group; Fig 2A). In contrast, activation within bilateral frontal cortex was markedly greater for controls than patients (main effect of group; Fig 2C). Interestingly, across all participants, the degree of frontal lobe engagement showed a strong negative correlation with posterior insular activity ($r(19)=-0.667$, $p=0.001$). As a group the patients showed a negative significant correlation ($r(3)=-0.886$, $p=0.045$), in degree of frontal activity and illness severity across all stimuli types.

We predicted that the patient group would be particularly sensitive to infestation-related stimuli (insects) presented on a background of skin, reflected in the critical interaction of group x object x background. Interestingly, this interaction also demonstrated discrete effects within bilateral frontal cortices. In particular, when viewing insects on skin, patients showed a marked deactivation compared to controls ($U(21)=22$, $p=0.040$) suggesting a deficit in the engagement of a region critical for cognitive control.

Neuroimaging results: IAPS images

At looking at both neutral and emotional images, patients compared to controls activated amygdala and parahippocampus, regardless of stimulus type (main effect of participant group). In the same contrast controls activated areas of frontal cortex

Behavioural Tasks

Interoception tasks

On the interoceptive accuracy tasks (mental tracking task), patients performed significantly poorer than controls ($t(16)=2.87$, $p = 0.011$); mean accuracy (\pm SEM) score patients 36.55% ($\pm 11.55\%$) and controls 69.51% ($\pm 4.32\%$) (Fig3a). Although there were no significant differences in subjective interoceptive sensibility (Porges Body Perception Questionnaire), we found significant difference in interoceptive trait prediction error: The patients showed a greater mismatch between objective accuracy and subjective sensibility than controls (patients 1.20 ± 0.95 , controls $-0.34, \pm 0.31$; $t(15)=2.08$, $p=0.028$) (Fig3b).

Rubber Hand Illusion

Patients were more likely to experience the illusion of ownership of the artificial limb: Objectively, patients showed significantly higher proprioceptive drift ($t(14)=2.21$, $p=0.044$) (Fig3c). On the questionnaire measures, agreement scores tended to be higher in the patient group than controls but none reached statistical significance.

Figure 3 here

DISCUSSION

We show for the first time how the processing of infestation-relevant stimuli is different in patients who experience abnormal skin sensations. We also show that these patients perform differently on measures of self-representation, i.e. interoceptive accuracy, interoceptive trait prediction area and susceptibility to the *rubber hand illusion*, as illustrated by proprioceptive drift.

The posterior insula / secondary somatosensory cortex was activated in both controls and in patients by images of skin (compared to leaf), with patients showing exaggerated responses. Posterior insula is functionally implicated as a primary interoceptive cortex. This early representation of the physiological state of the body projects to regions supporting negative emotional feelings, notably anxiety, including the right anterior insula and adjacent operculum where activity and volume predicts interoceptive accuracy and self-reported sensibility to internal sensations (Critchley, 2004). Moreover, the region is adjacent to part of the parietal lobe implicated in the sense of ‘corporeal awareness’ (Berlucchi and Aglioti, 1997) and somatic self-representation. Correspondingly, we observed behavioural differences between patients and controls in both interoceptive and somatic self-representation. Interestingly, this region is specifically implicated in the contagion of itchiness (Holle et al., 2012), where sensory experience arises from the inferential embodiment of another person’s sensation.

Across all conditions, patients showed heightened activity within the amygdala, particularly to images of insect on skin. This region is particularly associated with novel, salient, potentially threatening stimuli (LeDoux, 2000) and associated feeling states of fear and

anxiety. In parallel, across conditions, patients showed attenuated engagement of prefrontal areas that were robustly activated by controls. Within the constraints of our experiment, we interpret this finding from a perspective of affect regulation and sensory prediction: Prefrontal regions are critical to the cognitive control of emotional state including attention-dependent regulation, through detachment or reappraisal, of emotions (Ochsner et al., 2002). Plausibly, patients are less able to self-regulate responses to emotive stimuli and consequently experience intrusive thoughts and associated anxiety. Moreover, lateral prefrontal cortex is engaged during the experience of itch contagion (Holle et al., 2012), further highlighting relevance of top-down predictive influences on somatosensory control.

Across both groups, we also found that viewing insect-related images preferentially activates fusiform cortex extending into middle temporal cortex. This region is implicated in the representation and recognition of object categories and in cross-modal sensory associations (Martin and Chao, 2001). The proximity of this cluster to centres encoding biological motion and affective salience suggests that there may exist a functional neural module within human temporal cortex preferentially encoding arthropods with pathogenic potential, consistent with previous observations of heightened fusiform activation in spider phobia (Dilger et al., 2003).

The behavioural tasks revealed interesting differences in self-representation between patients and controls. We show for the first time that these patients are less accurate in their perception of internal bodily state than controls and demonstrate a mismatch between subjective interoceptive sensibility and objective interoceptive accuracy – interoceptive trait prediction error. This suggests that although they pay relatively more attention to changes in

bodily state, possibly as a consequence of a diminished capacity to predict and accurately sense bodily changes, this in turn may reinforce and maintain anxiety generated by abnormal skin sensations. This has implications for both anxiety (Paulus and Stein, 2006) and the integrity of self-representation (Seth et al., 2011).

We also report the novel finding that there is greater malleability in body ownership, as objective differences in proprioceptive drift evoked by the rubber hand illusion. While there is a need to establish causality, this malleability of self-representation may prove central to understanding psychopathological processes, as it has for other disorders, e.g. in a ‘comparator model’ of schizophrenia linking positive symptoms to problems in discriminating between sensations caused by the self, and sensory changes associated with external causes (Frith, 2011). An increase in the *rubber hand illusion* is relevant in this context because it reflects a greater weighting of external cues (from observing touch) over internal models of the body that depend, amongst other regions, on the right posterior insula/S2 (Peled et al., 2000, Germine et al., 2012). We do not show differences in the subjective measure of agreement for the rubber hand illusion, however it has been argued that these two measures (subjective agreement and objective drift) are dissociable (Rohde et al., 2011, Riemer et al., 2015).

Limitations of our study include small patient numbers, the presence of co-morbid depression in our patient sample and a lack of asynchronous condition in the rubber hand illusion paradigm. These patients represent a hard to recruit population and this is the first functional imaging investigation in a group of patients with abnormal skin sensations, and as such must be seen as exploratory. Unfortunately, we did not match the controls for levels of clinical or subclinical comorbid symptoms. Insula differences have also been reported in depression e.g.

(Lai and Wu, 2014). In our sample, differences in insula activity were only revealed in the contrast skin greater than leaf rather than in looking at emotional pictures as a whole, suggesting a state task specific activation rather than a trait phenomenon. In addition, patients with depression demonstrate altered interoceptive abilities in some studies e.g (Ehlers and Breuer, 1992, Wiebking et al., 2010). In our sample of patients with abnormal skin sensations, however, we demonstrate that not only do they exhibit poorer interoceptive accuracy, but also show greater interoceptive prediction error. We must acknowledge that low mood may well serve as a context for emergence of dermatological sensitivity and both may arise from core abnormalities in self-related processing, revealed by interoceptive abnormalities and interoceptive trait prediction error. This study is naturally limited in its capacity to establish causal relationships in between functional insular abnormalities, depressive symptoms, interoceptive deficits, self- representation and the expression of dermatological symptoms, and as such is exploratory.

From our findings, we propose a model in which there is dysfunctional interaction between posterior insular/parietal substrates for body schema and representations of potential infestation threats. The perceptual maintenance of abnormal skin sensations is reinforced by heightened salience through a failure of amygdala activity to habituate on account of diminished prefrontally-mediated capacity for appraisal and self-regulation. Together our experimental data reveal differences between patients experiencing abnormal skin sensations and controls, in both the central neural processing of infestation-relevant and emotional stimuli and in the representation of self.

Table 1

Age	Gender		Duration	Severity of current problem	Co-morbidities	Primary Symptom and subsequent inference
59	M	A	6 months	Not disclosed	none	Initially crawling sensation in skin. Developed after contact with person with possible scabies. Subsequent concern that may be infested with scabies.
68	F	B	20 years	3/10	depression	Initial and ongoing sensation of movement. Subsequently concern that may be fibres and hairs under skin.
48	F	C	7 years	10/10	past history cocaine misuse	Initial experience sensation of things biting her. Subsequently concern foreign bodies under skin.
47	F	D	9 years	6/10	depression	Initial abnormal skin sensation. Subsequent concern may be infested inanimate objects.
42	F	E	6 months	3/10	none	Initial strange sensations in body and skin. Subsequently worried they may represent calcium deposits.
47	F	F	3 months	0/10	depression	Initial strange sensations in skin. Subsequently concerned self and environment infested with moths.

Table 2

	Co-ordinates of peak	Region	cluster size (N voxels)	z
Skin/leaf; insect/non- insect				
Main effect insect vs non-insect	-46, -64, 8	Fusiform cortex extending into middle temporal gyrus	120	3.08
Main effect skin vs leaf	-24, -38, -34	Anterior cerebellum	77	3.22
	46, -20, 22	Insula and parietal cortex	71	3.05
	-20, 22, 50	Mid frontal	631	3.42
	32, 30, -18	Orbitofrontal	98	3.36
Main effect controls vs patients	16, 28, 56	Superior frontal	5574	4.28
	58, 2, 24	Pre-central frontal	65	3.09
patients vs controls	26, -2, -32	Amygdala and parahippocampus	74	3.41
Interaction patients vs controls (insect vs non-	No significant activation			

insect)				
controls vs patients (insect vs non-insect)	-36, 12, 48	Middle frontal gyrus	163	3.06
	-12, 32, 52	Superior frontal gyrus	672	2.97
patients vs controls (skin vs leaf)	-24, -36, -32	Anterior cerebellum	116	3.5
	44, -18, 20	Insula and parietal cortex	150	3.24
controls vs patients (skin vs leaf)	50, 40, 0	Frontal lobe including SFG, MFG, IFG and anterior cingulate	14,629	4.38
	-20, 48, -12	Superior frontal gyrus	71	2.87
3 way interaction (patients vs controls)	No significant activation			
3 way interaction (controls vs patients)	6, 64, -4	Medial orbitofrontal	1,279	3.62
IAPS images				
Main effect patients vs controls	26, -2, -32	Amygdala and parahippocampus	142	3.35

Controls vs patients	-28, 58, 20	Superior frontal gyrus	231	3.57
	2, 68, 16	Superior medial frontal gyrus	429	3.24
	52, 16, 14	Inferior frontal gyrus	103	3.02

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Figure 1

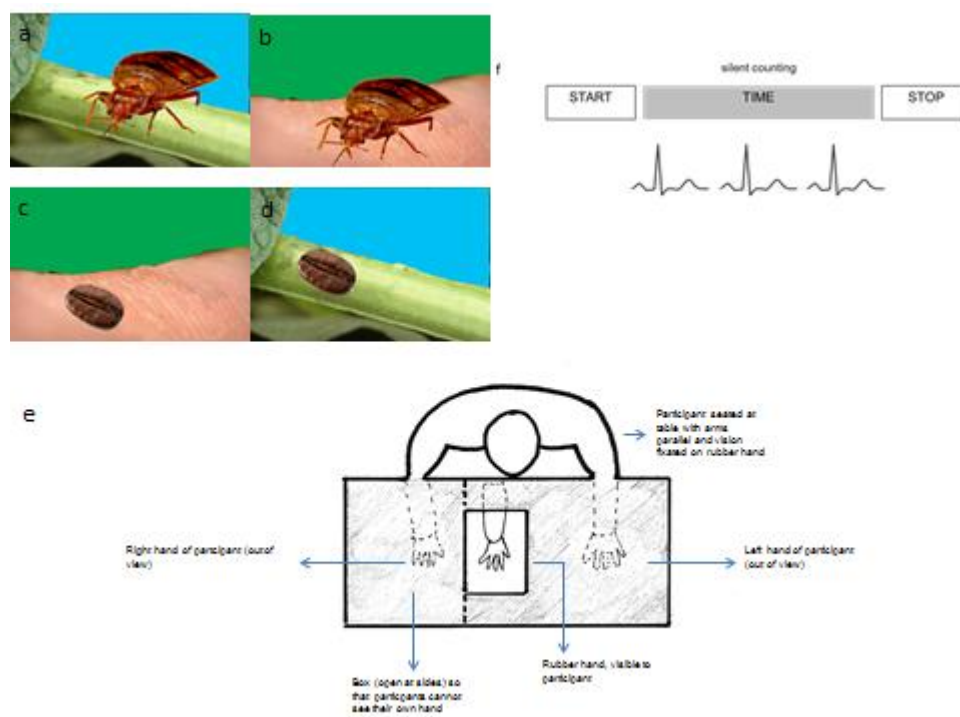
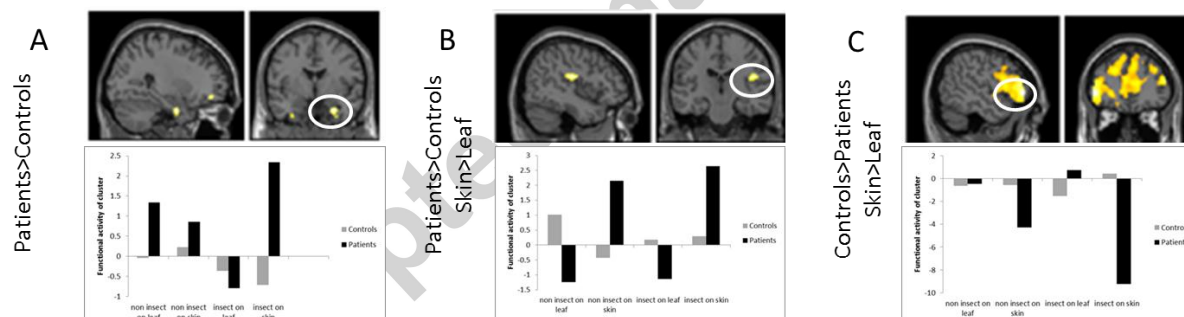


Figure 2



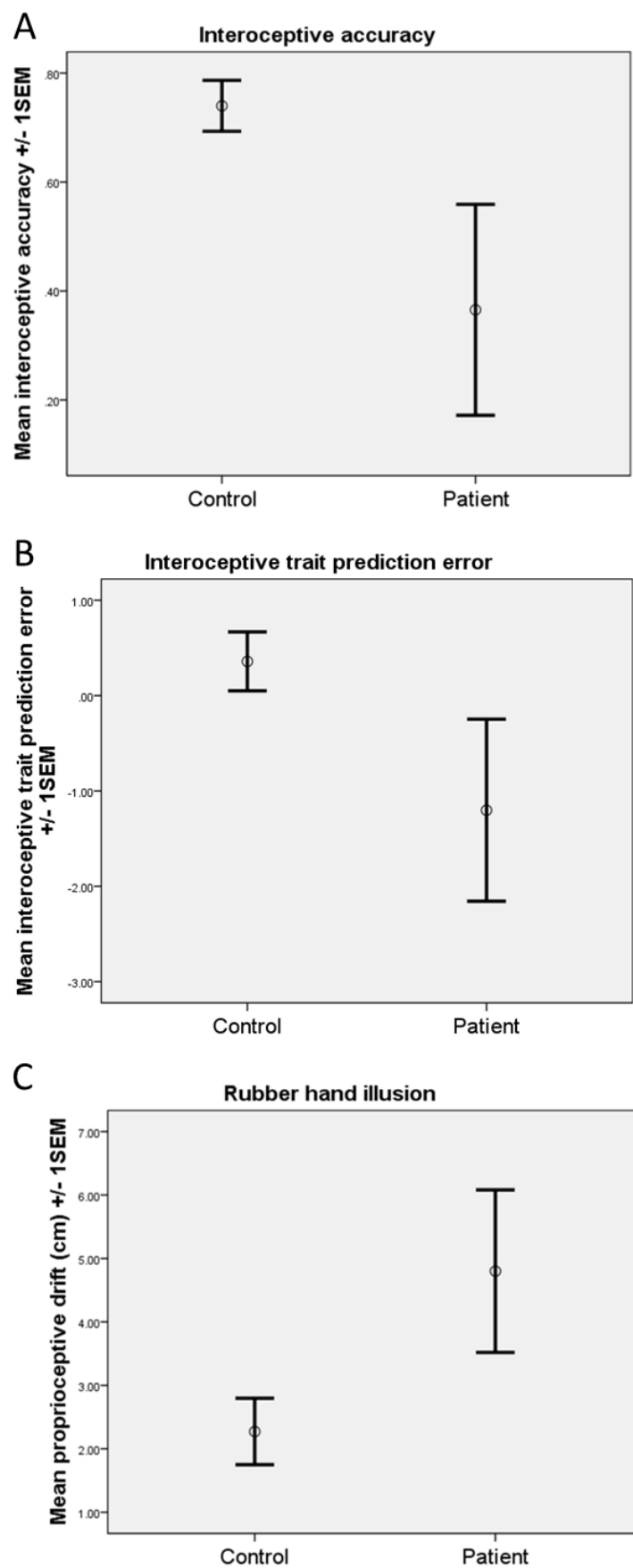


Figure 3

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Figure and Table legends

Figure 1

Figure showing tasks used in the experiment. 1a, 1b, 1c and 1d) Composite of insect and non-insect stimuli used in fMRI task, illustrating 2 x 2 x 2 factorial design: a)insect on leaf, b)insect on skin, c)non insect on skin, d)non insect on leaf. Images were presented for 4500ms, with an intertrial interval of 1500ms. 190 trials were performed, including interleaving null events. 1e demonstrates the procedure for the Rubber Hand Illusion task. 1f show interoceptive accuracy task where participants are asked to silently count their heartbeats over a period of time, presented in random order (25, 30, 35, 40, 45 and 50 s)

Figure 2

Contrast estimates showing main effect of presentation of insect versus non insect images, skin images rather than leaf, activation of controls compared to patients and patients compared to controls and the contrast of the 3 way interaction. All activation illustrated at a corrected threshold of $p < 0.05$ 2a)Brain activation in patients compared to controls across all conditions. Plot demonstrating differential response of brain activity centred at 26, -2, -32 (amygdala and parahippocampus) of patients and controls to the stimuli. Patients show stronger responses than controls in this area. 2b) Brain activation when viewing skin rather than leaf across in patients rather than controls, demonstrating activity in right insula centered at 44, -18, 20. Plot demonstrating differential response of brain activity in right insula of patients compared to controls viewing images of skin rather than leaf. 2c)Brain activation of controls more than patients looking at images of skin rather than leaf, demonstrating activity in orbitofrontal cortex (circled), with patients showing greater deactivation compared to controls particularly for images of insect on skin. Plot demonstrating differential response of

controls compared to patients viewing images of skin rather than leaf. Patients showed marked deactivation of this area compared to controls, particularly when viewing images of insects on skin

Figure 3

Charts illustrating differences between patients and controls on measures of self-representation. Error bars show one standard error of mean. 3A) illustrates decreased interoceptive accuracy in patients compared to controls. 3B) illustrates increased interoceptive trait prediction error in patients compared to controls. 3C) illustrates performance on *the rubber hand illusion*, with significantly greater proprioceptive drift in patients compared to controls.

Table 1. Patient characteristics demonstrating patient demographics, illness duration, illness severity, co-morbidities and phenomenology

Table 2. Table demonstrating brain activation across all contrasts including anatomical location, cluster size (k), MNI co-ordinates and Z score. All activation illustrated at corrected threshold of $p < 0.05$, minimum cluster size 64 voxels

ACKNOWLEDGMENTS

We acknowledge the financial support of The Sackler Centre for Consciousness Science, University of Sussex, UK and the invaluable assistance of Dr Simon Baker.

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Highlights:

- Functional neuroimaging of sensations of skin infestation is limited to a single case-report.
- This study provides the first neurobiological account of sensations of skin infestation
- We demonstrate abnormal fronto-limbic brain reactivity and self-representation.
- These findings could enhance understanding, increase physician and patient engagement.
- It may reduce stigma and provide insight into novel treatments.